## REMARKS

Applicants thank the Examiner for conducting an interview with applicants' representative. During the interview the Wood (Pharmacological Characterisation of the Human P2X4 Receptor Using FLIPR, Pharmacology Reviews and Communications, vol. 10, p. 341-347) and Tsuda (Mechanical Allodynia Caused by Intraplantar Injection of P2X Receptor Agonist in Rats: Involvement of Heteromeric P2X2/3 Receptor Signaling in Capsaicin-Insensitive Primary Afferent Neurons, Journal of Neuroscience, 2000, vol. 20, p. RC90/1-RC90/5) references were discussed. Amendments to claim 1 were discussed.

Claims 1 and 3 to 9 are in this application. Claims 10-41 have been withdrawn.

Claim 1 has been amended to include that the test compound is a selective inhibitor of an interaction of said P2X4 receptor agonist and P2X4 receptor. The basis for this amendment will be discussed below.

According to the Official Action, claims 1 and 3-9 are rejected as being anticipated under 35 USC 102(a) by Tsuda et al. (Nature, 14 August 2003, vol. 424, p. 778-783). This rejection is respectfully traversed.

Attached are the declarations of Akito Mizokoshi, Michael W. Salter and Yukari Shigemoto-Mogami in which these authors declare that they have reviewed the specification and claims of this application and they are not inventors of the subject matter claimed in this application. These declarations include the required statements regarding 18 USC 1001 and that all statements made by declarant are true. Therefore, since the remaining named authors are named as inventors of this application, the Tsuda reference is not citable as a reference as it is the inventors' own publication which was published less than one year prior to the filing date of this application.

Therefore, it is respectfully requested that the rejection be withdrawn.

According to the Official Action, claims 1 and 3-9 are rejected under 35 USC 103(a) as being unpatentable over Wood et al. (Pharmacological Characterisation of the Human P2X4 Receptor Using FLIPR, Pharmacology Reviews and Communications, vol. 10, p. 341-347) in view of Tsuda et al. (Mechanical Allodynia Caused by Intraplantar

Injection of P2X Receptor Agonist in Rats: Involvement of Heteromeric P2X2/3 Receptor Signaling in Capsaicin-Insensitive Primary Afferent Neurons, Journal of Neuroscience, 2000, vol. 20, p. RC90/1-RC90/5). This rejection is respectfully traversed.

As the Examiner stated in the Official Action, Wood et al. do not teach that the method of claim 1 can be used to identify compounds useful in the treatment of neuropathic pain, in particular, tactile allodynia induced after nerve injury.

The Tsuda, et al., reference cited above also does not teach or describe tactile allodynia.

Attached is a copy of THE MERCK MANUAL OF DIAGNOSIS AND THERAPY (17th edition) Section Neuropathic Pain, pages 1371-1372 (1999). This section clearly explains the difference between the two allodynia-mechanical and tactile allodynia. Regarding diagnosis and treatment of neuropathic pain, this dictionary describes on page 1372, left column, lines 7-12 "Deafferentation pain due to peripheral nerve damage must be distinguished from other forms of neuropathic pain in which an ongoing, potentially treatable pathologic process affects a peripheral nerve." Further, on page 1371, right column, lines 20-22, the term "deafferentation pain" is defined as a pain due to partial or complete interruption of peripheral or central afferent neural activity. Since the tactile allodynia disclosed on page 2, lines 31-32 of the present specification is due to peripheral nerve damage which usually causes partial or complete interruption of peripheral afferent neural activity, the tactile allodynia disclosed in the present specification is classified into the "deafferentation pain" in this dictionary. On the other hand, the mechanical allodynia taught by Tsuda et al., Journal of Neuro Science is due to a large amount of ATP released from damaged cells in an injured tissue. Such ATP-release due to tissue is usually an ongoing, potentially treatable pathologic process because an injured tissue can be usually treated. Therefore, the mechanical allodynia taught by Tsuda et al. is deemed as the "other forms of neuropathic pain" in the dictionary. Accordingly, the tactile allodynia disclosed in the present specification should be distinguished from the mechanical allodynia taught by Tsuda et al. in the context of therapy.

During the interview, amending claim 1 to limit the test compound to one that is a selective inhibitor of the $P2X_4$ receptor was discussed. The compounds tested in Wood are not selective inhibitors of the $P2X_4$ receptor. According to Wood, pyridoxalphopshate [sic]-6-azophenyl-2',4'-disulphuric acid (PPADS) and 4,4'-diisothiocyanatostilbene-2,2'-disulphonic acid are $P2X_4$ receptor inhibitors. However, these are not selective $P2X_4$ receptor inhibitors. Pyridoxalphopshate [sic]-6-azophenyl-2',4'-disulphuric acid (PPADS) is not a selective inhibitor of the $P2X_4$. This is based on the different results obtained in the experiments conducted in Tsuda et al., The Journal of Neuroscience, 2000, Vol. 20, pages 1-5 and this application. As explained in col. 2 on page 4 of Tsuda, the $P2X_{2/3}$ receptor is sensitive to PPADs. This is discussed further on page 24, line 22 to page 25, line 35 of this application where it is stated that PPADS is an antagonist of $P2X_r$ subtypes $P2X_{1,2,3,5,7}$ but not of $P2X_4$ and that doses of PPADs that should have been sufficient to increase Paw withdrawal threshold if the $P2X_4$ receptor involved in tactile allodynia were PPADS-sensitive.

DIDS (4,4'-diisothiocyanatostilbene-2,2'-disulphonic acid) is also not a selective inhibitor of the $P2X_4$ receptor. This is supported by the enclosed three documents: Ralevic et al. (Pharmacological Reviews, Vol. 50, No. 3, pp. 413-492, 1998), Bradford et al. (Biochem. J., Vol. 366, pp. 745-755, 2002), and Evans et al. (Molecular Pharmacology, Vol. 48, pp. 178-183, 1995) which are being filed with this response. Ralevic et al. reviews various findings for receptors of purines and pyrimidines including all of P2X receptors. Ralevic et al. describes in page 444, right column, lines 2-3 from the bottom that DIDS is a $Cl^-$ transport blocker. Relating to P2X receptors, Ralevic et al. describes in page 445, left column, lines 8-11 "DIDS discriminates between subtypes of P2X receptors, being a potent inhibitor of responses mediated at the $P2X_1$ receptor cloned from human bladder," and in page 445, left column, lines 17-18 "DIDS and some analogs of DIDS also block endogenous $P2X_7$-like receptors." Bradford et al. describes in page 748, left column, lines 44-46 that DIDS blocks effects of ATP on the $P2X_7$ receptor but not on the $P2X_4$ receptor. These descriptions teach that DIDS is a $Cl^-$ transport blocker, as well as a relatively potent inhibitor of the $P2X_1$ receptor or the $P2X_7$ receptor, but not of the $P2X_4$ receptor. In particular, Ralevic et al. describes in page 445, left column, line 11 that DIDS inhibits the $P2X_1$ receptor activity at $IC_{50}$ of 3 $\mu$M, which is demonstrated by experimental data found in Evans et al. (see Evans et al., page 181, Fig. 4a, and the same page, left column, lines 2-4 from the bottom; "the bladder smooth muscle form of the P2X receptor" in legend of Fig. 4 corresponds to the

$P2X_1$ receptor as indicated in Ralevic et al., page 447, the last two paragraph of left column). The $IC_{50}$ represents the concentration of a drug that is required for 50% inhibition of the receptor activity in vitro. On the other hand, the $IC_{50}$ value of DIDS for the $P2X_4$ receptor would be more than 30 $\mu$M on the basis of experimental data found in Wood et al. cited by the Examiner (see Wood et al., page 344, FIGURE 2). These data substantiate that DIDS inhibits the $P2X_1$ receptor activity much more strongly than the $P2X_4$ receptor activity, and thus, DIDS is not a selective inhibitor of the $P2X_4$ receptor.

Accordingly, the claimed method is not obvious over Wood et al. in view of Tsuda et al. and it is respectfully requested that the rejection be withdrawn.

It is submitted that the application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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